APPENDIX A: RESULTS OF ICF BIOTECHNOLOGY SURVEY

A. Purpose and Coverage of Survey

In 1988, ICF Incorporated conducted an OMB-approved telephone survey of companies involved in biotechnology in order to characterize the portion of the industry working in areas potentially subject to regulation under the Toxic Substances Control Act (TSCA). During the survey, ICF attempted to contact every company involved in TSCA-related biotechnology. The survey did not attempt to cover users of TSCA-related products such as farmers or waste treatment plant operators; in addition, universities were not surveyed.

Approximately 170 firms were contacted, of which 161 responded. Of the respondents, 72 reported that they were currently or expected to be working in market areas potentially subject to TSCA, and 89 reported that they were not involved in any of these areas.

Based on PMN data and trade publications, the survey coverage appears to be best for commercial recombinant products, especially intergeneric products. Coverage is likely to be lowest for companies working only with naturally occurring microorganisms and companies with a small amount of TSCA microorganism research confined to the laboratory.

The purpose of the survey was to collect information on the segment of the biotechnology industry that is potentially subject to TSCA. The major topics covered in the survey included:

- Financial Information, including total annual budget, sources of funds, overall R&D budget, proportion of R&D budget allocated to biotechnology and to TSCA-related products;
- Market Information, categorizing a company's TSCA products by end use market area;
- Product Characterization, noting the specific type of genetic manipulations, level of containment, and stage of development;
- New Uses, capturing a company's impressions of possible future applications and markets;

- Institutional Biosafety Committees (IBCs), including the size, labor requirements, and liability insurance needs; and

- Field Trials, determining the number of tests per microorganism and the number of microorganisms tested to develop one commercial product.

A copy of the survey was first sent to each company identified as a possible TSCA-related operation. Attachment 1 at the end of this appendix presents the survey questions. After the survey form had been received and reviewed by the appropriate company representative, an ICF employee telephoned the representative and recorded the responses to the questions. The responses were then incorporated into a computerized data base system.

B. Summary of Results

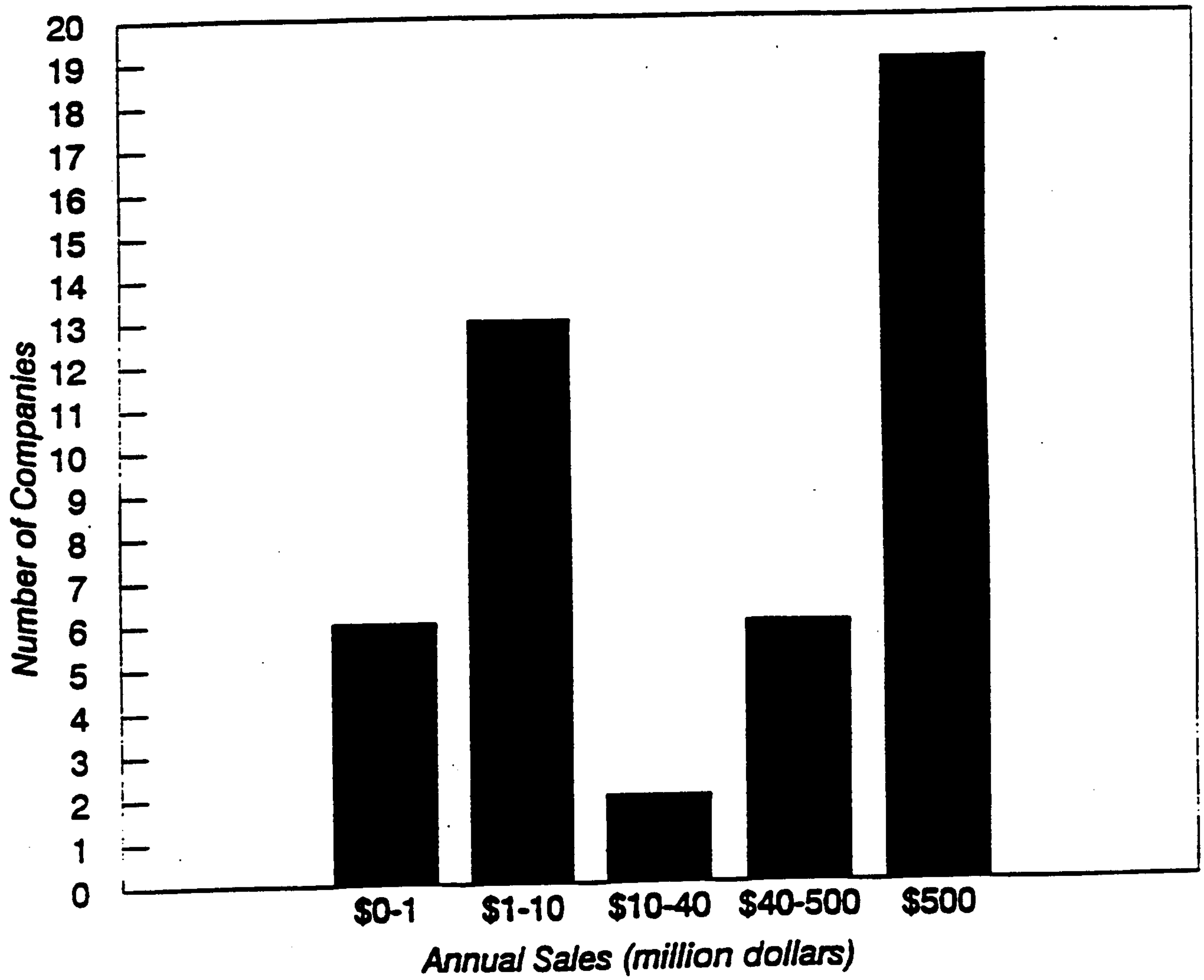
The response rate to the survey was generally high: most companies answered the majority of the questions. However, sample sizes vary throughout the results, because some companies selectively declined to answer certain questions. For example, about 20 percent of the firms did not provide specific financial information and some companies declined to characterize their products by type of genetic manipulation. The following seven sections summarize the results.

1. Financial Information

a. Annual Sales and Budgets

The North Carolina Biotechnology Center (NCBC) provided annual sales ranges when possible for each of the 172 companies in the survey population. Although some companies could not be assigned to a specific annual sales range, 68 firms could be classified as either small (33 firms) or large (35 firms). The companies identified in the survey divide sharply between small (sales less than $40 million each year) and large (sales of $40 million or more each year) firms. Figure A-1 presents the number of companies

Figure A-1. Annual Sales



Note: Data represents responses of 46 companies.

Source: ICF 1988.

in each range of annual sales. Of the 72 respondents, 46 could be categorized in one of the five sales ranges.

Profits from product sales were the most common source of companies' budgets, with 31 of the 69 responding companies listing profits as at least one source of funds. About 45 listed a single source of funds, 20 firms listed 2 sources, and 4 companies indicated 4 sources each. Table A-1 presents the sources of budget identified by the responding firms.

b. Research and Development Budgets

Additionally, firms were asked to provide information about their entire R&D budget (both biotechnology and other research), the portion of R&D budget allocated to biotechnology, and the portion allocated to TSCA-related products. Figure A-2 presents the percent of the respondents' R&D budgets devoted to all types of biotechnology (including TSCA and non-TSCA research areas). As shown in the figure, many small firms reported that they dedicate 100 percent of their R&D funds to biotechnology; respondents at most large companies, on the other hand, report that they allocate less than 20 percent of their R&D budget to biotechnology.[*] Figure A-3 presents the percent of reported biotechnology R&D budgets committed to products in TSCA-related market areas.

2. Market Information

The survey also asked firms to categorize products by market area and stage of development (i.e., commercial, currently in R&D, and expected in R&D within 5 years). The ten market areas (with examples) into which the firms classified their products include:

- Agricultural applications (e.g., fertilizers and nitrogen fixing microorganisms);

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[*] These percentages may apply only to the division or site surveyed rather than to the company as a whole.

Table A-1. Sources of Budget

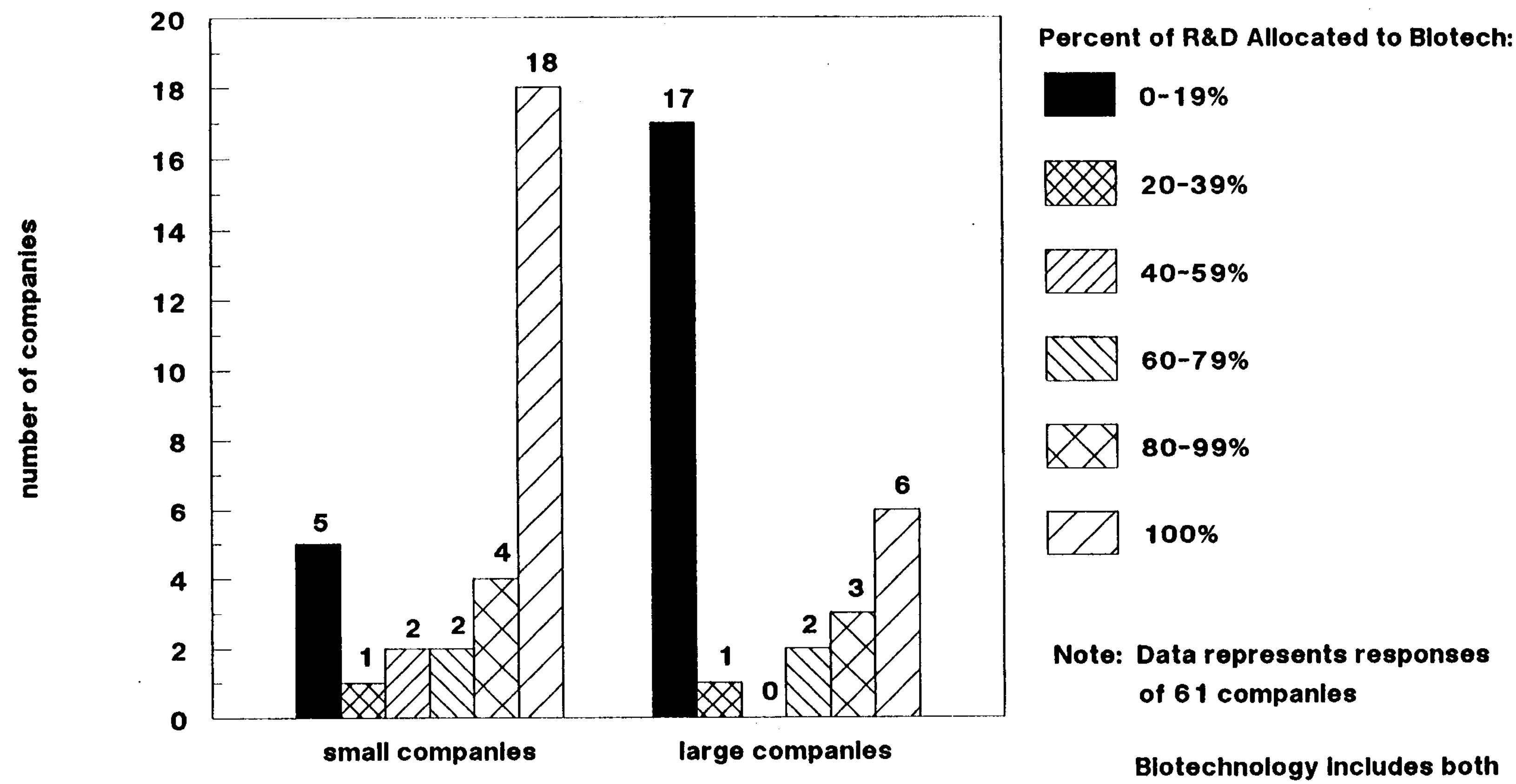
Source of Budget	Number of Firms
Profit From Products[a]	31
Parent Company Funds	21
Venture Capital	17
Stock Issues	14
Other Sources	14

Note: The total number of sources is greater than the 69 companies that responded because some firms listed more than one source.

[a] Profit from current products may include non-biotechnology products and non-TSCA biotechnology products.

Source: ICF 1988.

Figure A-2. Percent of R&D Allocated to Biotechnology versus Company Size

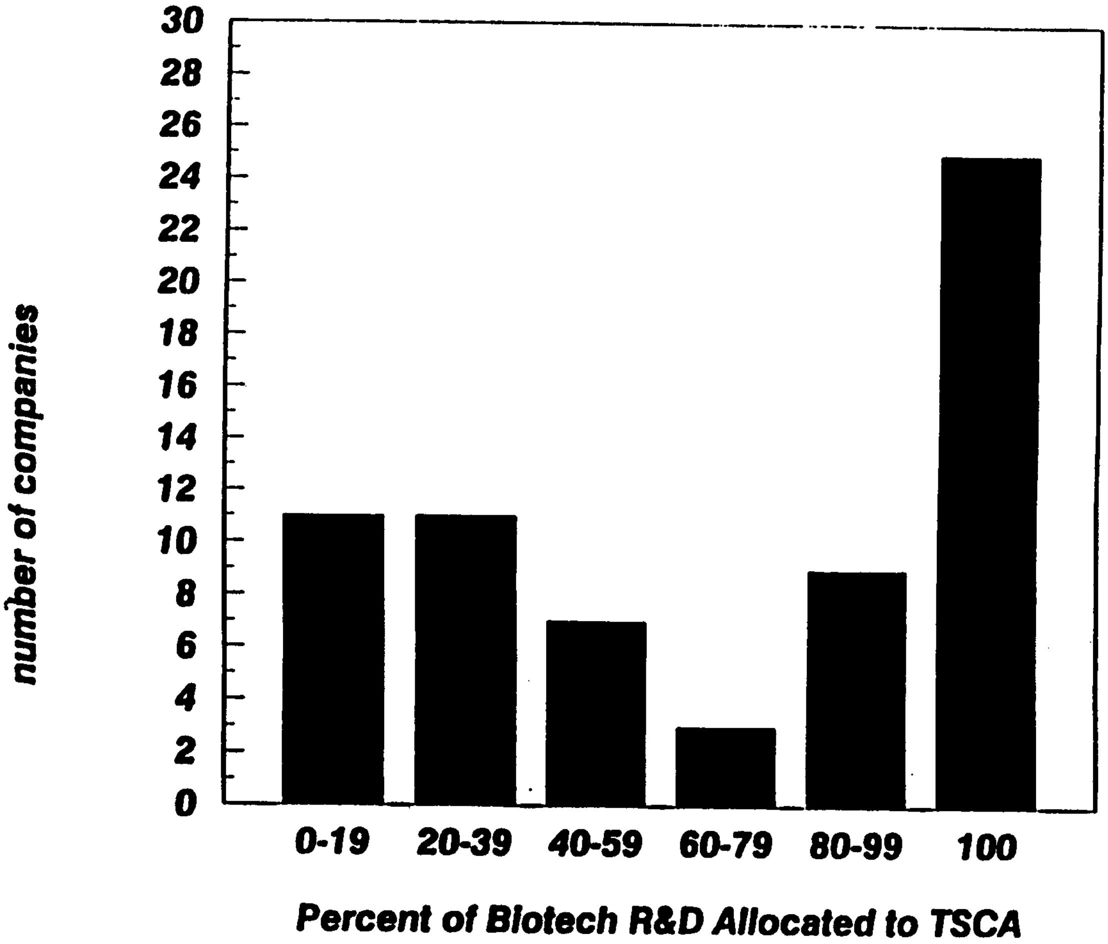


Note: Data represents responses of 61 companies

Biotechnology includes both TSCA-related and other non-TSCA research.

Source: ICF Biotechnology Survey 1988

Figure A-3. Percent of Biotechnology R&D at Responding Sites Committed to TSCA Products



Note: Data represents responses of 61 companies
Source: ICF 1988

- Biomass conversion (e.g., conversion of starch into ethanol);
- Energy applications (e.g., enhanced oil recovery);
- Commodity chemical production (e.g., mass production of acetic acid);
- Specialty chemical production (e.g., synthesis of industrial enzymes);
- Monitoring, measurement, and biosensors (e.g., use of bacteria to assay an area for the presence of toxic chemicals);
- Polymer and macromolecule production (e.g., production of fatty acids or glycerol);
- Waste treatment and pollutant degradation (e.g., the breakdown of chlorinated chemicals like PCBs); and
- Biotechnology reagents (e.g., products of engineered microorganisms for use in research).

Table A-2, based on Question II.1 in the survey, presents the number of products that are themselves microorganisms or are made using microorganisms classified by market area and stage of development. Fifty-nine companies responded to this question.

Firms also indicated how many of their products were being developed through a collaborative effort with another company through a research or licensing agreement or other joint venture. Thirty-two companies are engaged in collaborative efforts. Approximately 8.6 percent (or 197 products) were being developed through combined ventures. The survey data indicate that more large companies with sales greater than $40 million per year are involved in joint ventures than small firms.

3. Product Characterization

The matrix provided in Table A-3 more fully characterizes the products identified by the survey respondents. In addition, Figure A-4 provides a graphic representation of this information.

The survey was carried out in 1988, before the current regulatory text had been drafted. This fact and various accounting requirements required that a number of assumptions be made in order to use survey data to estimate the numbers of microorganisms that would fall into various rule categories for purposes of calculating industry and government costs. For example,

Table A-2. Products Classified by Market Area

Market Areas	Commercial	Currently in R&D	Expected in R&D Within 5 Years
Agricultural	121.0	49.5	39.5
Biomass Conversion	5.0	17.0	8.0
Energy Applications	0.0	10.0	9.5
Commodity Chemical Production	0.0	6.0	2.0
Specialty Chemical Production	173.0	74.0	128.0
Monitoring, Measurement, Biosensors	8.0	8.0	1.5
Mining and Metal Recovery	0.0	10.0	5.0
Polymer and Macromolecule Production	8.0	20.0	24.0
Waste Treatment and Pollution Degradation	175.0	60.0	74.5
Biotechnology Reagents	96.0	53.0	84.5
Other	3.0	3.0	0.0
Total	589.0	310.5	376.5

Note: Some companies represented their products as ranges; fractions reflect the average of these ranges.

Source: ICF 1988.

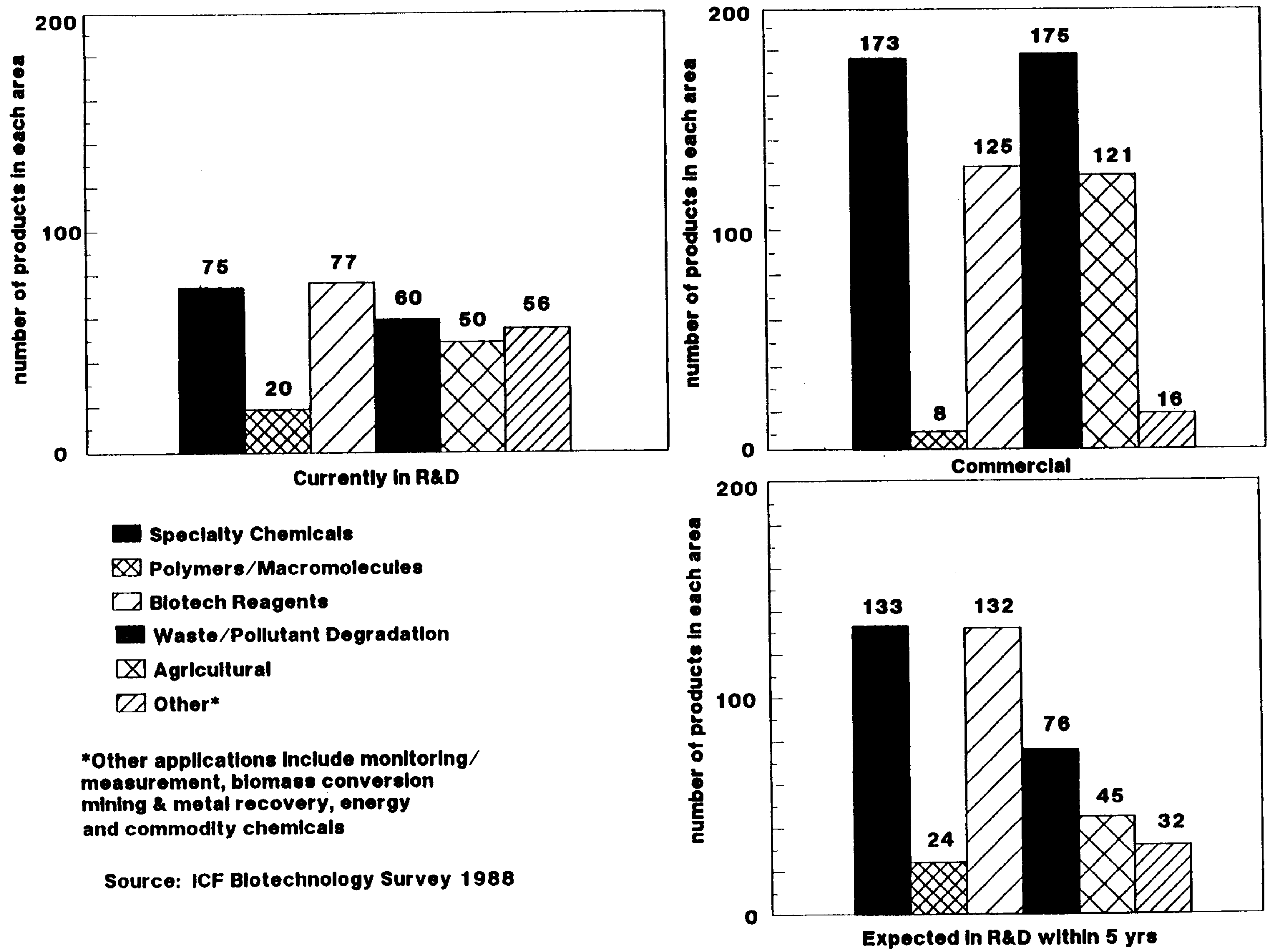
Table A-3. Product Characterization Matrix

TSCA Market Areas	rDNA, Intergeneric		rDNA, Intrageneric		Non-rDNA, Engineered		Naturally occurring	
	Contained	Released	Contained	Released	Contained	Released	Contained	Released
Agricultural Applications								
Commercial	0.0	0.0	0.0	0.0	0.0	1.0	9.0	111.0
R&D	6.0	10.0	3.5	1.5	1.5	1.0	15.5	10.5
R&D within 5 years	4.0	21.0	0.0	1.0	0.0	0.0	0.0	13.5
Biomass Conversion								
Commercial	0.0	0.0	0.0	0.0	1.0	0.0	4.0	0.0
R&D	2.0	0.0	3.0	0.0	2.0	0.0	10.0	0.0
R&D within 5 years	4.5	0.0	0.0	0.0	0.0	0.0	3.5	0.0
Energy Applications								
Commercial	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
R&D	2.0	0.0	0.0	0.0	1.0	1.0	3.0	3.0
R&D within 5 years	1.5	0.0	1.5	0.0	2.5	0.0	1.5	2.5
Commodity Chemical Production								
Commercial	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
R&D	1.0	0.0	1.0	0.0	1.0	0.0	3.0	0.0
R&D within 5 years	1.0	0.0	1.0	0.0	0.0	0.0	0.0	0.0
Specialty Chemical Production								
Commercial	4.0	0.0	12.0	0.0	56.0	0.0	101.0	0.0
R&D	22.0	0.0	9.0	0.0	26.0	0.0	17.0	0.0
R&D within 5 years	44.5	0.0	23.0	0.0	23.5	0.0	37.0	0.0
Monitoring and Measurement								
Commercial	5.0	0.0	0.0	0.0	0.0	0.0	3.0	0.0
R&D	2.0	1.0	0.0	0.0	0.0	0.0	5.0	0.0
R&D within 5 years	0.0	0.0	0.0	0.0	0.0	0.0	1.5	0.0
Mining and Metal Recovery								
Commercial	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
R&D	1.5	0.0	1.5	0.0	1.5	1.0	2.5	2.0
R&D within 5 years	2.0	1.0	0.0	0.0	0.0	1.0	0.0	1.0
Polymer/Macromolecule Production								
Commercial	0.0	0.0	6.0	0.0	0.0	0.0	2.0	0.0
R&D	1.5	0.0	7.5	0.0	3.5	0.0	7.5	0.0
R&D within 5 years	2.5	0.0	14.0	0.0	3.5	0.0	4.0	0.0
Waste and Pollution Degradation								
Commercial	0.0	0.0	0.0	0.0	0.0	0.0	3.0	172.0
R&D	4.5	0.0	0.0	0.0	0.0	0.0	11.0	44.5
R&D within 5 years	11.5	2.5	2.0	2.0	2.0	2.0	6.0	46.5
Biotechnology Reagents								
Commercial	36.5	0.0	12.0	0.0	12.0	0.0	35.5	0.0
R&D	27.0	0.0	3.0	0.0	8.0	0.0	15.0	0.0
R&D within 5 years	27.5	0.0	18.0	0.0	19.0	0.0	20.0	0.0
Other								
Commercial	0.0	0.0	0.0	0.0	0.0	0.0	1.0	2.0
R&D	0.0	0.0	0.0	0.0	0.0	0.0	0.0	3.0
R&D within 5 years	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Total	214.0	35.5	118.0	4.5	164.0	7.0	321.5	411.5

Note: Some companies represented their products as ranges; fractions reflect the average of these ranges.

Source: ICF 1988.

Figure A-4. Products in Each TSCA Market Area



*Other applications include monitoring/ measurement, biomass conversion mining & metal recovery, energy and commodity chemicals

Source: ICF Biotechnology Survey 1988

in Table A-3, some of the numbers suggest "half" microorganisms. This accounting method was used to count the microorganisms in the survey data whose characterization was ambiguous. In these cases, the microorganism was divided in half and placed into two categories. Other assumptions used to predict the number of submissions are explained in Appendix C.

The table indicates the level of containment and type of genetic manipulation for each class of product. The total number of products in the matrix is less than the total provided in Table A-2, because not every company that identified products elected to characterize them. This is especially true in the cases of products expected in R&D within 5 years and biotechnology reagents that were difficult to characterize.

Forty companies responded to the part of the question concerning current commercial products; 57 companies responded concerning products in R&D; and 36 companies responded concerning products expected in R&D in five years.

Several points should be kept in mind in interpreting the survey figures.

- Apparent growth rates may have been affected by incomplete responses from companies not estimating the number of future R&D products

- Companies may have used differing definitions of "product." For example, a "product" might be a single strain, a research project covering several strains, a mixture of microorganisms, a chemical derived from a microorganism, or a kit containing such chemicals.

- The lack of commercial products reported in the survey for energy and commodity chemicals may have resulted from survey undercoverage, nonresponses, or reporting of these products in other, overlapping categories. As Chapter II explains, some energy-related and commodity chemicals uses have reached the commercial stage.

- Most or all reagents reported as "commercial" may qualify as "research" under TSCA because they are sold only for R&D uses.

- The definitions of "contained" used by survey respondents may differ from the Final Rule definitions.

- Microorganisms still in laboratory R&D but intended for eventual release may have been reported as "contained" by some respondents and as "released" by others.

Companies also provided information on the percentage of the microorganisms that are considered pathogenic.* Five of the 72 companies responding used pathogenic organisms. Approximately 64 products were described as pathogenic. In addition, firms working with rDNA manipulations indicated the percentage that "involve the use of regulatory regions (e.g., promotor, terminator, etc.)" (ICF 1988). The survey identified 17 companies which produce a total of 134.5 rDNA products characterized as involving only regulatory regions.** A few firms indicated that it was technically impossible to use only regulatory regions without affecting any coding regions.

4. New Uses

Companies were asked to indicate the likelihood that they would apply their existing products to new market areas after the initial commercialization of the product. As Figure A-5 illustrates, 36 of the 72 companies responded that they foresaw a greater than 50 percent chance of entering new market areas, while 17 firms indicated a 50 percent chance. Another 17 firms were less optimistic, indicating a less than 50 percent chance that they would enter new market areas.

Most survey respondents were optimistic about the opportunity for additional applications for the same products within current market

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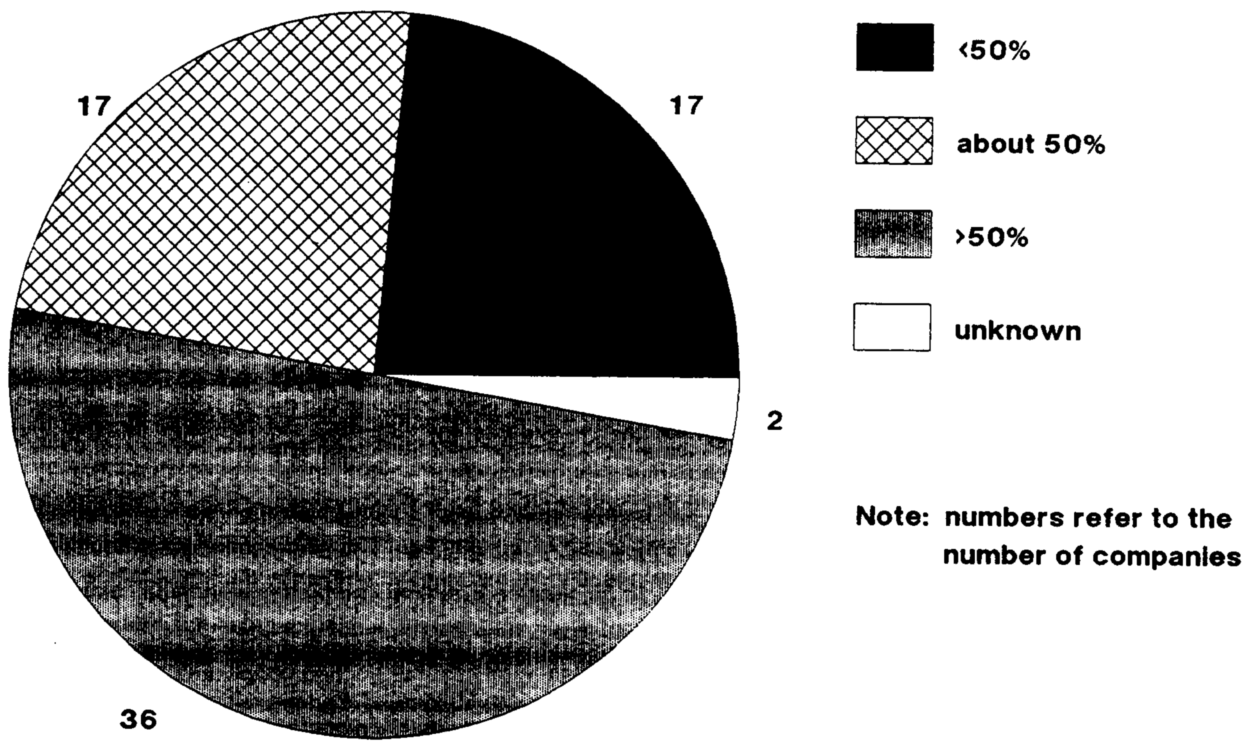
Pathogenicity may be an indication of the inherent risk of certain microorganisms and therefore may be of significance regarding the level of concern on the part of the Agency.

Some companies represented their products as ranges; fractions or products reflect the average of these ranges.

Figure A-5. Chance of Additional Market Areas for Existing Products



areas.* As indicated in Figure A-6, 60 firms indicated that they anticipated new applications for their products within current market areas, 10 firms did not expect new applications, and 2 firms did not know.

5. Institutional Biosafety Committees (IBCs)

Institutional Biosafety Committees (IBCs) are currently used by the National Institute of Health (NIH), universities, and private companies to implement NIH guidelines for research involving recombinant DNA microorganisms. The IBCs are responsible for reviewing research proposals using rDNA technology to ensure proper containment of recombinant organisms and the safety of laboratory personnel. IBCs may also perform other functions, including oversight of research using infectious disease agents, hazardous chemicals, or radioactive materials, but these activities may be outside of the biotechnology arena.

Approximately 44 percent of the firms surveyed reported having an active IBC. Some firms did not have an IBC because they were not involved in recombinant DNA projects. Table A-4 presents the information on firms that have an IBC and provides statistics on the amount of time involved in IBC decision making. The average membership was 7, with a minimum of 3 members and a maximum size of 15 members. Thirteen firms listed the amount of time needed to reach a decision on levels of containment; The average was 58 days, with a low estimate of 9 days and a high estimate of 1 year. Many firms felt that the amount of time required for an IBC decision depended on the complexity of the issue before the committee. As the industry gains more experience, it is expected that IBCs will review experiments more efficiently and therefore decrease the time required to come to a decision. Of the firms

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An example of two applications for one product within the waste treatment market area is the degradation of two different types of waste by the same microorganism.

Figure A-6. Opportunity for Additional Applications for the Same Products Within Current Market Areas

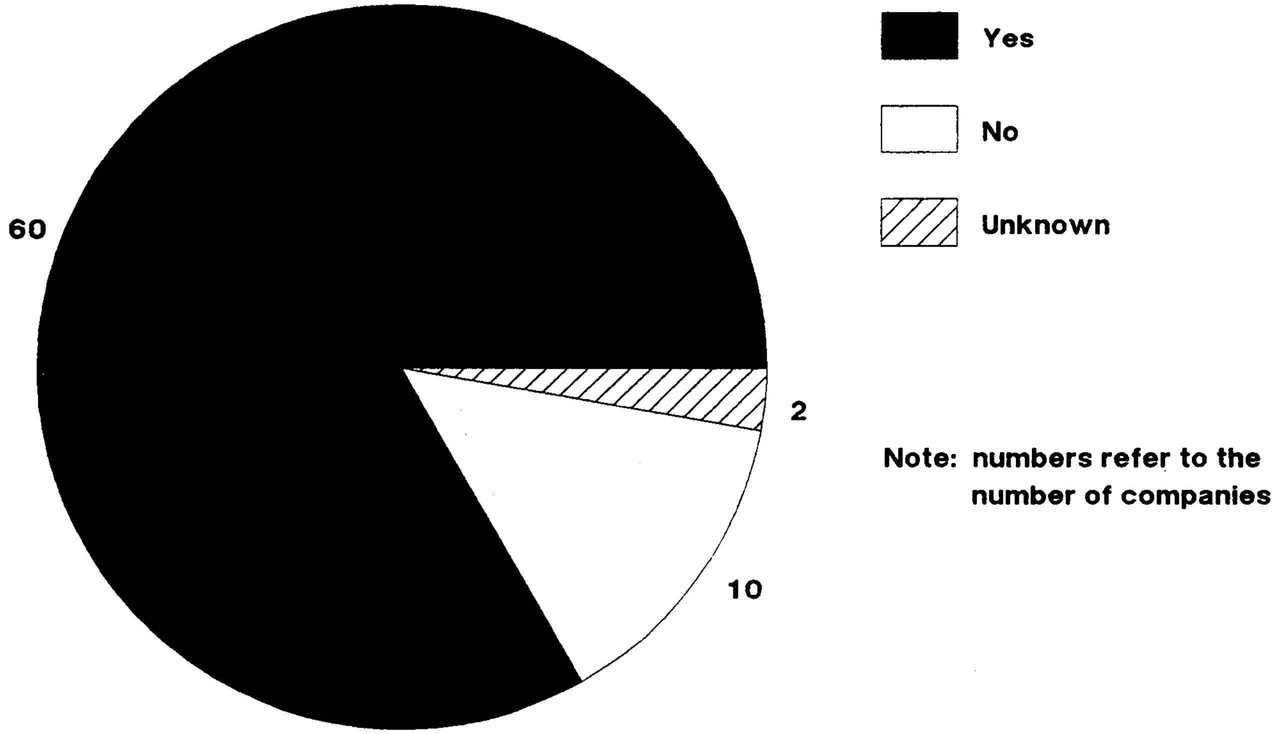


Table A-4. Institutional Biosafety Committees

Number of IBC Members[a]	Hours of Discussion per Case	Total Time to Reach a Decision (days)
--	30.0	--
3.0	--	--
3.0	1.0	--
3.0	--	--
3.0	365.0	--
4.5	--	--
5.0	--	--
5.0	30.0	22.5
5.0	--	--
5.0	--	--
5.0	--	10.0
5.0	20.5	60.0
5.5	--	8.5
6.0	--	--
6.0	30.0	72.0
6.0	20.0	48.0
7.0	--	--
8.0	--	--
8.0	--	--
8.0	28.5	10.5
8.5	17.0	45.0
9.0	--	--
9.0	--	--
9.0	37.5	18.0
10.0	30.0	--
10.0	--	--
10.0	6.5	
9.0		
10.0	--	--
15.0	30.0	37.5
15.0	30.0	40.0

[a] Some companies represented their IBC memberships as ranges; fractions reflect the average of these ranges.

Source: ICF 1988.

surveyed, only one company had separate liability insurance for its IBC. The annual premium was $70,000 for coverage of $1 million.

6. Field Trials

For many applications of microorganisms, it may be necessary to introduce microorganisms into the environment after laboratory trials have been completed. The survey addressed the issue of field releases to determine the number of different microorganisms that would be tested and the number of field tests each product would undergo in the development of one commercial product.

Only firms with released products need to conduct field tests of their products, implying that field testing is applicable to 33 of the surveyed firms. The average number of microorganisms field tested per company is 5, based on the average of the estimates of the 25 firms that responded to this question. Table A-5 presents the number of tests per microorganism and the number of microorganisms tested to develop one commercial product.

Of the roughly 420 microorganisms that were field tested, as reported by the 25 companies responding to the survey, roughly 91 percent (383) were naturally occurring, 8 percent (33) were recombinant DNA (32 intergeneric and one intrageneric) and 1 percent (4) were non-rDNA engineered. Seventeen of the 25 responding firms expected no change in the number of field tests per microorganisms, 6 firms expected an increase in the number of field tests, and 2 anticipated a decrease in the number of field tests over time as familiarity with the requirements of product development improved the field testing process.

7. Delays in Product Development

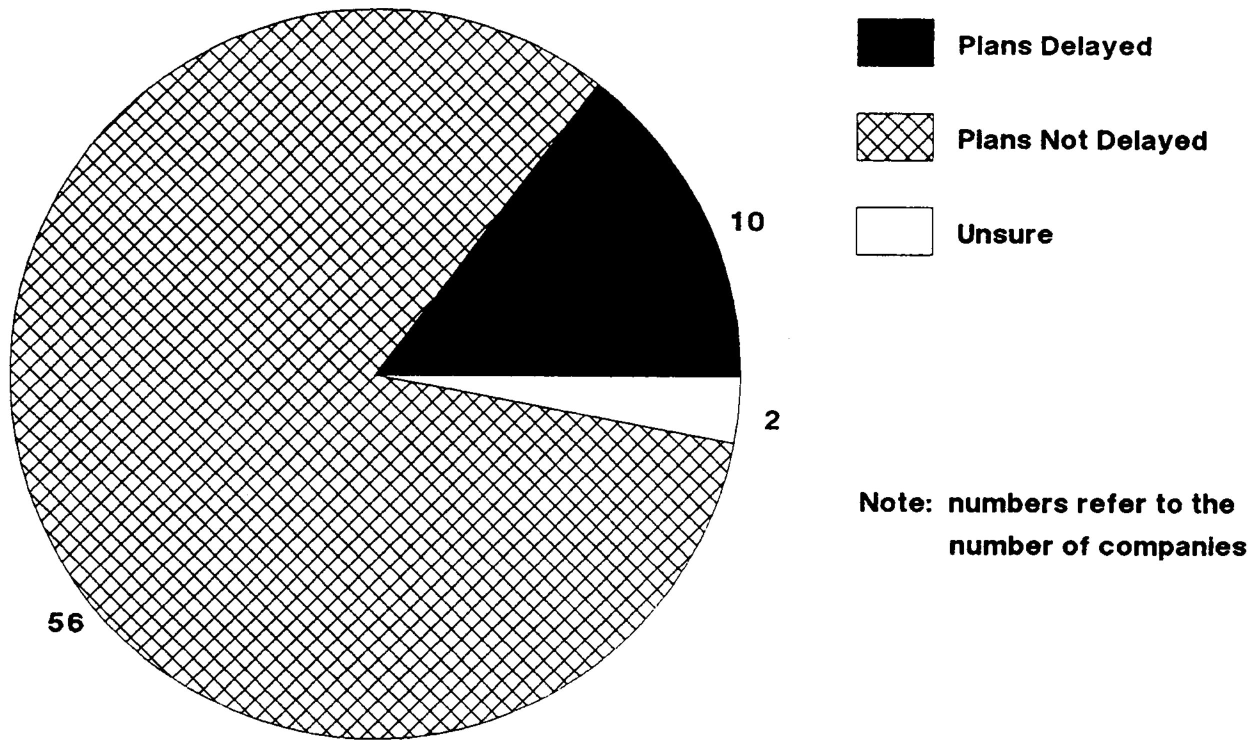
Figure A-7 illustrates the responses of the 68 companies that indicated whether their development plans had been delayed due to the lack of regulation in place for microorganism uses in TSCA-related market areas. Over

Table A-5. Field Tests

Number of Organisms Tested	Number of Field Tests per Organism	Anticipated Change in Number of Field Tests
--	1.0	Increase
0.0	0.0	Remain Constant
1.0	4.0	Remain Constant
1.0	4.0	Remain Constant
1.0	--	Decrease
1.0	--	Remain Constant
1.0	1.0	Remain Constant
1.0	10.0	Remain Constant
1.0	7.5	Increase
1.0	5.5	Increase
1.5	--	--
2.0	4.0	Remain Constant
3.0	2.0	Remain Constant
3.5	3.0	Remain Constant
4.0	8.0	Increase
5.0	5.0	Decrease
5.5	75.0	Remain Constant
6.0	6.0	Remain Constant
7.0	5.5	Remain Constant
7.5	--	Remain Constant
8.0	--	Increase
10.0	3.0	Remain Constant
10.0	3.0	Remain Constant
12.5	3.5	Increase
12.5	12.5	Remain Constant
20.0	12.5	Remain Constant

Source: ICF 1988.

Figure A-7. Delay of Product Development Plans



86 percent (56 firms) felt their plans had not been delayed. On the other hand, 10 firms indicated their development plans had been delayed because of the lack of regulation in place, and 2 companies were unsure how this affected their development plans. By comparison, of the companies performing fieldtests, 74 percent of companies felt that development plans had not been delayed. For all companies experiencing delays, roughly 42 percent were working with naturally occurring microorganisms, 25 percent with intergeneric microorganisms, 14 percent with intrageneric microorganisms, and 19 percent with non-rDNA engineered microorganisms. For those companies involved in the field testing of microorganisms, roughly 36 percent were working with naturally occurring microorganisms, 29 percent with intergeneric microorganisms, 21 percent with intrageneric microorganisms, and 14 percent with non-rDNA engineered microorganisms.

C. <u>Microbial Applications Subject to TSCA Jurisdiction</u>

Results from the 1988 survey and from other sources suggest that several market areas dominate TSCA microbial applications in terms of numbers of products. These areas are specialty and commodity chemical production*, reagents production, microorganisms released into the environment for waste degradation, and microorganisms released for agricultural applications such as nitrogen fixation on crops. Results from the ICF survey, summarized in Figure A-4, Table A-6, and Table A-3, show these categories as accounting for the large majority of companies and products. The remainder of this chapter describes specific microorganism applications which fall under TSCA jurisdiction. Information in the following sections came from a variety of

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"Specialty chemicals" is a broad category encompassing low-volume, high-value added products. "Commodity chemicals" are large volume products with typically low unit prices. These categories cut across other categories discussed below, such as Biopolymers or Agricultural products.

Table A-6. Market Sector Profiles for Biotechnology Companies

Market Sector	Number of Companies[a]	Number of Products[b]
Biotech Reagents[c]	23	201
Specialty Chemicals	21	248
Waste Degradation	21	235
Agricultural Applications	17	171
Polymer/Macromolecule Production	9	28
Biomass conversion	10	23
Monitoring, Measurement	10	16
Mining/Metal Recovery	8	10
Energy	9	9
Commodity Chemicals	5	8
Other	5	6

[a] The number of companies in the table exceeds the total number of companies identified by the survey as potentially subject to TSCA (72 firms) because some companies work in several market areas. In addition some companies working with naturally occurring microbes may have been inadvertently excluded from the survey.

[b] The product numbers include both microorganisms and products of microorganisms, as well as products sold commercially and current R&D products for the firms responding to the ICF survey.

[c] Most or all reagents listed may be used only for contained research.

Source: ICF 1988.

sources including the 1988 ICF survey, public docket information for pastmicrobial PMNs, industry directories, company literature, the trade press, and conversations with industry representatives.

1. <u>Specialty Chemicals</u>

As Table A-7 shows, many microorganisms are used to produce specialty chemicals. Most of the closed-system PMNs received by the Agency have been for the production of enzymes.* In 1988, the leading TSCA commercial application in this area was microorganism production of enzymes used as detergent additives. Enzymes from microorganisms are also used in the production of fuel ethanol, paper, textiles, and leather, and for waste treatment and cleaning. Microorganisms are also used to produce biopolymers (discussed below) and pesticide intermediates (Novo 1986, Kidder 1984, Bioscan 1990, Shamel and Chow 1988).

One company described three stages in developing and producing a large volume enzyme (Norman 1989, 1990a, 1990b):

- The first stage involves several years in laboratory development. This research is likely to involve culture quantities of up to 10 liters and to be conducted in accordance with National Institutes of Health (NIH) guidelines for containment (NIH 1986).

- The second stage involves pilot plant production for 6 months to 3 years or more, using much larger fermentors, e.g. 4,000 liters. At this stage, the company determines whether large scale production will be profitable and produces samples for customers to test. These pilot fermentors do not necessarily follow the physical containment specifications designated as NIH BL-LS (NIH 1986). As many as 40 percent or more of products may drop out at this stage rather than going on to commercial production.

- The third stage is large scale commercial production, using very large fermentors, e.g. 17 million or 40 million gallons. For some industrial enzymes, products in the same batch may be sold for both TSCA and non-TSCA uses.

"Specialty chemicals" are low volume, high value substances, and could include some chemicals discussed below under "polymers and macromolecules." Enzymes are proteins which catalyze chemical reactions.

Table A-7. "Contained" Microorganisms and Products of Microorganisms by Type of Manipulation

	Phase of Development		
	Commercial	Research and Development	Expected in R&D Within 5 Years
Specialty Chemicals			
rDNA intergeneric	4	22	44.5
rDNA intrageneric	12	9	23
Non-rDNA, Engineered	56	26	23.5
naturally occurring	101	17	37
Total	173	74	128
Commodity Chemicals[a]			
rDNA intergeneric	-	1	1
rDNA intrageneric	-	1	1
Non-rDNA, Engineered	-	1	-
naturally occurring	-	3	-
Total	0	6	2
Polymers and Macromolecules[a]			
rDNA intergeneric	-	1.5	2.5
rDNA intrageneric	6	7.5	14
Non-rDNA, Engineered	-	3.5	3.5
naturally occurring	2	7.5	4
Total	8	20.0	24.0
Biotech Reagents[b]			
rDNA intergeneric	36.5	27	27.5
rDNA intrageneric	12	3	18
Non-rDNA, Engineered	12	8	19
naturally occurring	32.5	15	20
Total	93.0	53	84.5

Note: Respondee definitions of "contained" may have differed from the Final Rule definitions. Some products were represented as ranges; fractions of products represent the average of these ranges.

[a] Some chemicals in this category may have been reported in other categories or may not have been reported due to non-responses on some questions.

[b] Reagents sold only for research are considered R&D chemicals under TSCA. One company, reporting 900 reagent products was excluded from the count because an unknown portion of it's products were not microbially produced.

Source: ICF 1988 (see Table A-3).

Table A-7. "Contained" Microorganisms and Products of Microorganisms by Type of Manipulation (continued)

	Phase of Development		
	Commercial	Research and Development	Expected in R&D Within 5 Years
Waste and Pollution Degradation			
rDNA intergeneric	-	4.5	11.5
rDNA intrageneric	-	-	2
Non-rDNA, Engineered	-	-	2
naturally occurring	3	11	6
Total	3	15.5	21.5
Agricultural Applications			
rDNA intergeneric	-	6	4
rDNA intrageneric	-	3.5	-
Non-rDNA, Engineered	-	1.5	-
naturally occurring	9	15.5	-
Total	9	26.5	4
Mining and Metal Recovery			
rDNA intergeneric	-	1.5	2
rDNA intrageneric	-	1.5	-
Non-rDNA, Engineered	-	1.5	-
naturally occurring	-	2.5	-
Total	-	7	2

Note: Respondee definitions of "contained" may have differed from the Final Rule definitions. Some products were represented as ranges; fractions of products represent the average of these ranges.

Source: ICF 1988 (see Table A-3).

2. Commodity Chemicals

Commodity chemicals are high-volume, low-value added products. Microorganisms are used commercially to produce several commodity chemicals which have at least some TSCA applications. These include fuel ethanol, citric acid for household detergents and other uses, and gluconic acid for cleaning compounds (Novo 1986). In 1988, one company announced plans to produce lactic acid through fermentation for uses that may include plastics production (Chemical Marketing Reporter 1989).

Other commodity chemicals such as glycerol, acetic acid, and acrylic acid can be produced by microorganisms. However, according to an article published in 1988, it is much less expensive to synthesize them through chemical means from petrochemical feedstocks. Microorganism production would not be cost-competitive unless oil prices rose sharply or improvements were made to the fermentation process (Shamel and Chow 1988). Fuel ethanol is widely produced using fermentation only because of government subsidies.

Table A-7 shows no products to be in commercial production for this category at the time of the survey. However, survey coverage was incomplete, and some products may have been reported in other, overlapping categories. For example, survey respondents may have listed fuel ethanol applications under "biomass conversion," since ethanol is produced through fermentation of biomass such as cornstarch. Thus, the Agency believes that there are several commercial producers involved in this market area.

3. Polymers and Macromolecules

Biopolymers are biologically-produced polysaccharides or other chemicals made up of repeating subunits. Macromolecules include fatty acids and glycerol. Enzymes also may be included in this category. Depending on their markets and uses, biopolymers and macromolecules could also be classified as specialty chemicals, commodity chemicals, or reagents.

An important biopolymer is xanthan gum, a microbially-produced polysaccharide (made up of sugars) used in commercial applications which include enhanced oil recovery. Other microbial biopolymers are being researched for uses in adhesives, industrial coatings, biodegradable plastics, recovery of heavy metals from waste streams, oil cleanup, and waste treatment. (ICF 1989, Chemical Week 1990, Bioscan 1989, 1990, Ouellette and Cheremisinioff 1985, OTA 1984). Many of these biopolymers also could be isolated from genetically modified microorganisms. For example, in 1988, Synergen was conducting recombinant research on microorganisms that produce xanthan gum (Bioscan 1989, Bioprocessing Technology 1989).

4. Reagents and Monitoring/Measurement Products

Biotechnology reagents comprise a broad product category that includes enzymes, plasmids, living cells and other biological substances sold for molecular biology research and analytic uses. Reagents used in non-medical diagnostic applications also can be classified as monitoring/measurement products.

When reagents are sold for uses that fall under TSCA jurisdiction, any microorganisms used in their production also are considered to fall under TSCA jurisdiction. If reagents are sold purely for research, and meet the eligibility requirements for the "small quantities" research exemption under TSCA §5(h)(3), they would not be reportable. However, some reagents are sold for non-R&D uses such as routine detection of bacterial contaminants in food or measurement of biocide effectiveness in water (Stewart 1990).

Microorganisms used to produce these reagents may be subject to the same TSCA reporting requirements as other commercial-stage microorganisms.*

The 1988 survey identified a large number of reagent products in R&D and commercial use (see Table A-7). The survey did not show whether any of these reagents were sold for non-research uses. At the time the survey was conducted, only one PMN for reagent production had been received: the PMN was for a microorganism to produce a growth factor. Additionally, EPA had received inquiries from several manufacturers concerning reagent applications for non-research uses. As a result, it seems likely that most reagents reported in the survey are for research uses.

5. Waste Treatment and Bioremediation **

Microorganism waste treatment and degradation of toxic pollutants at contaminated sites (bioremediation) are major environmental uses of living microorganisms for TSCA applications, as indicated in Table A-8. Inoculants derived from microorganisms -- cultures of living organisms -- are added to waste treatment tanks, drains, septic tanks, or contaminated sites to supplement normal biological degradation.

No data were collected on the number of sites using these inoculants for waste treatment. However, in 1988, there were a large number of locations where inoculants derived from microorganisms were either used or could be used in the future, including municipal and industrial waste treatment facilities, restaurants and other facilities requiring drain or other degreasing, and some

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When this analysis was prepared, it was not completely certain that EPA had jurisdiction over microbes used in food quality control analysis.

Bioremediation involves removing hazardous or toxic substances; whereas bioreclamation involves reclaiming reusable materials.

Table A-8. "Released" Products by Type of Manipulation and Market Area

	Phase of Development		
	Commercial	Research and Development	Expected in R&D Within 5 Years
Waste and Pollution Degradation			
rDNA intergeneric	-	-	2.5
rDNA intrageneric	-	-	2
Non-rDNA, Engineered	-	-	2
naturally occurring[a]	172	44.5	46.5
Total	172	44.5	53
Agricultural Applications			
rDNA intergeneric	-	10	21
rDNA intrageneric	-	1.5	1
Non-rDNA, Engineered	1	1	-
naturally occurring	111	10.5	13.5
Total	112	23	35.5
Mining and Metal Recovery			
rDNA intergeneric	-	-	1
rDNA intrageneric	-	-	-
Non-rDNA, Engineered	-	1	1
naturally occurring	2	2	1
Total	2	3	3
Other Released Applications			
rDNA intergeneric	-	-	-
rDNA intrageneric	-	-	-
Non-rDNA, Engineered	-	-	-
naturally occurring	2	3	-
Total	-	-	-

Note: Respondee definitions of "released" may have differed from that in the Final Rule. Some products were represented as ranges; fractions of products represent the average of these ranges.

[a] Some products described as naturally occurring may have been developed originally using deliberate mutagenesis (Davis 1990). Waste treatment uses of naturally occurring microbes may have been significantly understated.

Source: ICF 1988 (see Table A-3).

fraction of the 1000-plus Superfund sites on EPA's priority cleanup list.*

Respondents to the ICF survey, in 1988, reported that all waste treatment microorganisms sold for environmental use were naturally occurring. However, exposing microorganisms to toxic chemicals for the purpose of selecting cells best able to degrade the chemicals may accelerate mutation. This type of exposure also may encourage selection of microorganisms that have received plasmids from other species or even other genera. For this reason, the line between "naturally occurring" and "genetically modified" microorganisms may not be readily discernible. In addition, at the time of the survey, while few if any inoculant suppliers appeared to be using deliberate mutagenesis techniques to develop products, some "naturally occurring" microorganisms designed for waste treatment may be descendants of strains originally developed in the laboratory through deliberate mutagenesis (Davis 1990, Hood 1990).

None of the companies surveyed in 1988 reported that they were conducting genetic engineering research for waste treatment applications. However, in 1988, the Agency was aware of research projects at universities and within the industry aimed at developing recombinant microorganisms for toxic waste degradation. For example, General Electric was developing a recombinant microorganism to degrade polychlorinated biphenyls (PCBs) (Mondello and Yates 1988). Researchers were also investigating recombinant microorganisms that degrade trichloroethylene (TCE), benzene, toluene, and other toxic substances (Olsen 1989).

The most likely use of microorganisms developed using techniques that would be subject to the Final Rule is to degrade toxic pollutants that are

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* Bioremediation can also be conducted by adding oxygen and nutrients to encourage the growth of microorganisms already present in soil or groundwater. This application would not be affected by the rule and is not discussed here.

recalcitrant to normal biological degradation. For example, bacteria and fungi have been discovered that can degrade a wide variety of substances, including microorganisms that can degrade at least 75% of the top pollutants listed on Dutch priority pollutant lists, described as closely resembling the U.S. EPA priority list (Witholt 1989). However, when the survey was conducted, the use of recombinant microorganisms for waste treatment had not yet advanced beyond the laboratory, and EPA had not received PMNs for waste degradation microorganisms. More recent experience has indicated that researchers are beginning to investigate intergeneric microorganisms for use in waste treatment bioremediation.

Table A-9 lists some examples of microorganisms that work alone or together in a consortium[*] to degrade pollutants, together with the types of toxic substance they can degrade. According to one source (Chemical Week 1986), bioremediation offers several economic and environmental advantages over conventional treatment techniques:

- on-site waste treatment that avoids transportation costs and risks;
- minimum site disruption;
- permanent degradation of waste;
- lower cost than other treatment methods; and
- faster degradation than air stripping or carbon adsorption.

Incineration is usually a more rapid means of destroying toxic contaminants than bioremediation, but involves the transportation of large quantities of contaminated material (i.e., soil). Incineration typically has a process capacity of about 100 tons per day; whereas, biodegradation can take

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[*] A consortium is a group of individual microorganism strains with affinities for complimentary substrates that can be used to degrade waste. The consortium can often degrade contaminants that no single strain alone can degrade.

Table A-9. Examples of Biodegradative Organisms

Substrate to Degrade	Microorganism
PCBs	Pseudomonas, Aeromonas, Achromobacter, Alcaligenes, Enterobacter, Bacillus
PCP, p-cresol	Flavobacterium, Pseudomonas
Alachlor	Streptomycete Isolate 5
Parathion (Two-step process)	Flavobacterium and Pseudomonas
2,4,5-Trichloroxphenolxyacetic acid	Pseudomonas cepacia
2,2-dichloropropionate	Pseudomonas putida
4-EB	Pseudomonas
Aromatics	Acinetobacter, Pseudomonas
Chlorobenzenes	Pseudomonas putida and P. alcaligenes

Sources: Bonitz 1988, Lindow 1989.

4 to 5 months to eliminate the same amount of hazardous material from the same 100 tons (Bonitz 1988). Conversely, at the time of the survey, the cost of incineration ranged from $250 to $500 per ton of material processed, while bioremediation costs were estimated at only $40 to $70 per ton (Bonitz 1988). Bioreclamation costs generally ranged from $8,000 to $12,000 per ton of contaminant removed as compared to air stripping costs that ranged from $30,000 to $40,000 per ton and carbon adsorption costs that ranged from $80,000 per ton of contaminant removed (Chemical Week 1986).

Nevertheless, bioremediation and bioreclamation have some inherent limitations, because they rely on living organisms to degrade waste. The following factors may sometimes reduce the attractiveness of biotreatment: target contaminants may not be sufficiently soluble in water and thus not available to the microorganism; some contaminants may not be susceptible to biodegradation while for others, microorganisms that degrade them have not been identified; the concentration of contaminants may be too high or to too low for successful biotreatment; and at temperatures below 50°F, the metabolism of a given bacterium may be too slow to work effectively (Chemical Week 1986, Bonitz 1988, Lindow 1989).

6. <u>Nitrogen Fixation and Other Agricultural Releases</u>

TSCA regulates certain agricultural applications of microorganisms that are not covered under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), including nitrogen fixation agents, algal soil conditioners, intermediates used in the production of pesticides (a closed system application), and microorganisms tested in the environment for potential use as pesticides.

In 1988, microbial nitrogen fixation was the major TSCA agricultural application of biotechnology involving release of living microorganisms. Nitrogen-fixing microorganisms transform (or "fix") atmospheric nitrogen into a biologically useful form. In agriculture, nitrogen fixation involves symbiotic associations between the roots of legume crops such as alfalfa and soybeans, and microorganisms such as Rhizobium and Bradyrhizobium species (Lindow 1989). Nitrogen fixation can reduce the amount of nitrogenous fertilizer required for crops capable of fixing nitrogen (e.g., legumes) and crops grown in rotation with legumes, such as corn. It has also been suggested that the ability to fix nitrogen could through genetic engineering be introduced into crop plants that currently are unable to fix nitrogen (e.g., corn).

By 1988, EPA had received 19 voluntary PMNs for field tests of genetically engineered strains for nitrogen fixation, all from BioTechnica International* or a subsidiary. Twelve strains of genetically engineered microorganisms had actually been field tested by the company. In addition, at least one company had begun test marketing a commercial nitrogen fixing strain created through conventional mutagenesis (McCormick 1988, Bioscan 1990).

Another environmental application is the release of biopesticide precursors for ecological studies. For example, at the time the survey was conducted, Monsanto had submitted a voluntary PMN to the Agency for a Pseudomonas aureofaciens strain intended to ultimately become a biopesticide, but lacking pesticidal properties. The purpose of the field trial, conducted at Clemson University, was to test a genetic marker as a method for tracking the microorganism and studying the survival and movement of the bacteria in the soil. A third agricultural application is use of microscopical algae (Paisely 1989) and mycorrhizal fungi for soil enrichment.

All 19 PMNs reviewed were from BioTechnica International. Subsequent to this analysis, BioTechnica International changed its name and is now known as Research Seeds.

In the 1988 survey, agricultural applications were the second largest use of released microorganisms, after waste treatment. The overwhelming majority of commercial products reported by survey respondents involve naturally occurring microorganisms.

7. Energy, Mining, and Other Released Uses

Microorganisms may be released for mining, metal recovery, and energy applications.* In these areas, the 1988 survey reported very few released products in commercial use, under development, or expected in R&D, either for naturally occurring or altered microorganisms (See Table A-8). However, a literature search suggests that there could be considerable interest in the use of microorganisms such as *Thiobacillus* for mining and fuel desulfurization applications (Science News 1990).

Microorganisms have been used to recover and concentrate metals in mining applications (Finnerty and Singer 1983). The actions of some microorganisms that are found naturally associated with ores increase the acid solubility of metals such as copper and uranium, thus aiding their leaching and recovery from low-grade ores. Although bioprocessing is a slow, passive process, approximately 10 percent or 200 million pounds of U.S. copper and about 0.8 million pounds of uranium were produced in 1985 using this method (Brierley 1985).

Microorganisms can be used in a leaching process to recover coal at lower costs without reducing the coal's heating value (Ouellette and Cheremisinoff 1985). Microorganisms may also be used to extract sulfur from coal, making it less polluting (OTA 1984). Other energy applications include oil desulfurization and denitrogenation as well as methods for enhancing oil,

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* Certain contained energy applications are treated in other sections of this chapter, such as commodity chemicals (fuel ethanol) or biopolymers (xanthan gum for oil industry applications).

gas, shale, and sand tar recovery. For example, a pseudomonas-like microorganism has been isolated that is capable of converting sulfur-andnitrogen-containing compounds in oil to easily removed, water soluble compounds (Ouellette and Cheremisinoff 1985).

Microorganisms may also be used to enhance oil recovery. In 1988, traditional oil extraction techniques left over half of the oil in the ground. Microbial Enhanced Oil Recovery (MEOR) relies on injecting microbes that produce polymers and surfactants that loosen up the trapped oil and mobilize it toward the producing wells. At the time of the survey, this technique had been applied on single oil wells, but large scale application had not been attempted (Bryant and Burtchfield 1989). Table A-10 presents examples of microbes that may be used in energy applications.

D. <u>University Research in TSCA Market Areas</u>

Most university research with "new" microorganisms appears to be confined to the laboratory. As of August 1990, the Agency knew of only two university field tests of microorganisms in TSCA applications that would bedefined as "new" under the Final Rule (see Chapter I).* These two tests were voluntarily submitted to EPA for review by their corporate sponsors, using PMNs. In one case, a researcher at Louisiana State University supervised the field testing of four genetically engineered <u>Rhizobia</u> strains developed by BioTechnica International (Breitenbeck 1989). In another, Clemson University field tested a genetically engineered microorganism developed by Monsanto as part of a pesticides research program (EPA 1989).

Other TSCA application areas for university microbial research include microbial ecology, waste degradation, biomass conversion, mining and metal recovery, and energy-related applications. The examples given below are not

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* A third field test, of an Intergeneric <u>Rhizobium</u> bacterium, was planned by Eric Triplett of the University of Wisconsin (Fox 1990).

Table A-10. Examples of Microbes Used in Energy Applications

Genus	Products
Clostridium	Gases, acids, alcohols, and surfactants
Bacillus	Acids and surfactants
Pseudomonas	Surfactants and polymers
Xanthomonas	Polymers
Leuconostoc	Polymers
Desulfovibrio	Gases, acids, and sulfur-reducing functions
Arthrobacter	Surfactants and alcohols
Corynebacterium	Surfactants
Enterobacter	Gases and acids

Source: Bryant and Burchfield 1989.

meant to be exhaustive, but to illustrate some of the types of research in TSCA market areas performed at universities.

Research underway in basic microbial ecology includes techniques for detection, enumeration, and identification of microorganisms in the environment. EPA's Office of Research and Development is funding research in this area, including possible future releases of genetically engineered microorganisms (EPA 1989). For example, researchers at Oregon State University and the University of Illinois, in collaboration with the USDA Agricultural Research Service, were developing novel methods for tracking genetically engineered <u>Agrobacterium</u> <u>radiobacter</u> in agricultural ecosystems. In 1988, this research involved both contained and field releases of genetically engineered <u>Agrobacterium</u> strains (EPA 1989).

Another area of research is toxic waste treatment. In 1988, one university research team used recombinant <u>Pseudomonas</u> <u>cepacia</u> to degrade aromatic hydrocarbons (Chakrabarty 1989, Loper 1989). Another team (Klein 1989) was involved in characterizing plasmids in aerobic and anaerobic microorganisms for the degradation and immobilization of toxic wastes.

Mining and metal recovery is another TSCA market area receiving attention in the university community. At the time of the survey, one researcher was developing active stains of recombinant <u>Thiobacillus</u> <u>ferrooxidans</u> for future releases in the environment for the solubilization and recovery of metals including copper and uranium (Holmes 1989).

1. <u>Final Rule Effects on Reporting</u>

It seems possible that in the future, the number of university releases of "new" microorganisms in TSCA applications could be at least as significant as the number of industry releases. However, even in the absence of the rule, some of these expected university field experiments may be reviewed by other agencies that have provided funding to the institution for rDNA research, such as the National Institutes of Health or the U.S. Department of Agriculture. Hence, EPA reporting requirements under TSCA may increase the amount of university reporting only in cases where a company or commercial interest has provided rDNA funding or where the construct does not fall within NIH's definition of "recombinant." EPA has not determined the number of such cases.

ATTACHMENT 1. THE ICF BIOTECHNOLOGY SURVEY FORM

COVER SHEET

COMPANY NAME: ______________________________

COMPANY CONTACT: ______________________________

TELEPHONE NUMBER: ______________________________

COMPANY SURVEY NUMBER: ___________

TELEPHONE SURVEY QUESTIONNAIRE FOR BIOTECHNOLOGY
REGULATORY ANALYSIS DATA INPUT
(OMB NO. 2070-0034)

Interviewer: ____________________ Date: ____________________

Company Number: ______

1. Do you manufacture or intend to manufacture products that are microorganisms or are made using microorganisms? ____(yes/no)____

I. **FINANCIAL INFORMATION**

1. What is the source of your budget?

   -- Venture capital __________
   -- Parent company __________
   -- Stock issues __________
   -- Profit from current product lines __________
   -- Other -- please specify __________

2. What is your company's total annual budget? ______________

3. What is your company's total annual R&D budget? __________

4. What proportion of your R&D budget is allocated to biotechnology?

   ____

5. When planning for a new product, what level of potential total profits from a particular product do you consider a minimum necessary for your company to continue to develop that product?

   -- <$50,000 __________
   -- $50,000-$100,000 __________
   -- $100,000-$250,000 __________
   -- $250,000-$500,000 __________
   -- $500,000-$1,000,000 __________
   -- $1-$5 million __________
   -- $5-$10 million __________
   -- >$10 million __________

Company Number: __________

II. MARKET INFORMATION

The EPA proposed biotechnology rule pertains to market areas regulated under the Toxic Substances Control Act (TSCA). Those market areas include a wide-range of agricultural, industrial, and environmental uses. The following list outlines the market areas regulated under TSCA.

1. How many of your company's products that are in each of the following TSCA areas and are microorganisms or made using microorganisms are commercial, currently in R&D, or expected to be in R&D within 5 years.

TSCA Market Areas	Commercial	Currently in R&D	Expected in R&D Within 5 Years
Agricultural (e.g., fertilizers, nitrogen fixation, but NOT pesticides)	___	___	___
Conversion of Biomass (e.g., conversion of starch into alcohol)	___	___	___
Energy (e.g., enhanced oil recovery)	___	___	___
Commodity Chemical Production (e.g., mass production of acetic acid)	___	___	___
Specialty Chemical Production (e.g., synthesis of industrial enzymes)	___	___	___
Monitoring/Measurement/Biosensor (e.g., use of bacteria to assay an area for a certain toxic chemical)	___	___	___
Mining/Metal Recovery (e.g., solubilization (leaching) of metals from ore by bacteria)	___	___	___
Polymer/Macromolecule Production (e.g., production of fatty acids or glyerol)	___	___	___
Waste/Pollutant Degradation (e.g., the breakdown of PCBs)	___	___	___
Biotechnology Reagents (e.g., products of engineered organisms as products for lab use)	___	___	___
Other -- please define	___	___	___

Company Number: __________

II. <u>MARKET INFORMATION</u> (Continued)

2. How many of those products listed under Question 1 were or are being developed through a collaborative effort with another company (e.g., research agreement, licensing agreement, or joint venture)?

3. What proportion of your biotechnology R&D budget is committed to the products described above (i.e., to TSCA market areas)? ________________

Company Number: ________

III. BIOTECHNOLOGY PRODUCT CHARACTERIZATION

This section is intended to more fully characterize those products discussed in the previous section. The characterization of those products will be based on the following descriptors: whether the microorganism is contained or released and the type of genetic manipulation (if any) the microorganism in question has undergone.

For survey purposes, contained refers to microorganisms that are not intended for release and may be used in the manufacture of products that are not themselves microorganisms (e.g., microorganisms used in fermentors to produce enzymes) and released refers to microorganisms that are intended for use in the environment.

The genetic manipulation descriptors are:

-- Naturally occurring,
-- Non-rDNA engineered (e.g., chemical mutagenesis),
-- rDNA Intrageneric, or
-- rDNA Intergeneric.

1. On the following page is a matrix that categorizes each product and potential product by the technology used to develop the microoroganism (rDNA intergeneric, rDNA intrageneric, non-rDNA engineered, or naturally occurring), whether the microorganism is contained (con) or released (rel), and the stage of development for each market area. Please indicate approximately how many products your company is developing for any applicable description.

NUMBER OF PRODUCTS THAT ARE MICROORGANISMS OR MADE USING MICROORGANISMS

	rDNA, INTERGENERIC		rDNA, INTRAGENERIC		NON-rDNA, ENGINEERED		NATURALLY OCCURRING	
	CON	REL	CON	REL	CON	REL	CON	REL
Agriculture								
Commercial	___	___	___	___	___	___	___	___
R&D	___	___	___	___	___	___	___	___
In R&D Within 5 Years	___	___	___	___	___	___	___	___
Conversion of Biomass								
Commercial	___	___	___	___	___	___	___	___
R&D	___	___	___	___	___	___	___	___
In R&D Within 5 Years	___	___	___	___	___	___	___	___
Energy								
Commercial	___	___	___	___	___	___	___	___
R&D	___	___	___	___	___	___	___	___
In R&D Within 5 Years	___	___	___	___	___	___	___	___
Commodity Chemical Production								
Commercial	___	___	___	___	___	___	___	___
R&D	___	___	___	___	___	___	___	___
In R&D Within 5 Years	___	___	___	___	___	___	___	___
Specialty Chemical Production								
Commercial	___	___	___	___	___	___	___	___
R&D	___	___	___	___	___	___	___	___
In R&D Within 5 Years	___	___	___	___	___	___	___	___
Monitoring/Measurement/Biosensor								
Commercial	___	___	___	___	___	___	___	___
R&D	___	___	___	___	___	___	___	___
In R&D Within 5 Years	___	___	___	___	___	___	___	___
Mining/Metal Recovery								
Commercial	___	___	___	___	___	___	___	___
R&D	___	___	___	___	___	___	___	___
In R&D Within 5 Years	___	___	___	___	___	___	___	___
Polymer/Macromolecule Production								
Commercial	___	___	___	___	___	___	___	___
R&D	___	___	___	___	___	___	___	___
In R&D Within 5 Years	___	___	___	___	___	___	___	___
Waste/Pollutant Degradation								
Commercial	___	___	___	___	___	___	___	___
R&D	___	___	___	___	___	___	___	___
In R&D Within 5 Years	___	___	___	___	___	___	___	___
Biotechnology Reagents								
Commercial	___	___	___	___	___	___	___	___
R&D	___	___	___	___	___	___	___	___
In R&D Within 5 Years	___	___	___	___	___	___	___	___
Other — Please Define								
Commercial	___	___	___	___	___	___	___	___
R&D	___	___	___	___	___	___	___	___
In R&D Within 5 Years	___	___	___	___	___	___	___	___

Company Number: __________

III. **BIOTECHNOLOGY PRODUCT CHARACTERIZATION (Continued)**

2. Of the products described on page 6, approximately what percentage could be characterized as pathogenic? For survey purposes standard pathology references indicate the types of microorganisms considered pathogenic.

3. Of the products described on page 6 that involve rDNA manipulations, approximately what percentage involve the use of regulatory regions (e.g., promotor, terminator, etc.)?

IV. **NEW USES**

1. What do you think is the likelihood that additional market areas will be discovered after commercialization of any of your products?

   -- <50 percent ________
   -- Approximately 50 percent ________
   -- >50 percent ________.

   For the following question, the term "applications" refers to different uses within a particular market area. For example, degradation of two different types of waste would be two different applications of a product within the waste degradation market area.

2. Do you expect that additional applications for the same market area for any given product will be discovered after initial commercialization of that product? ________________ If yes, how many? __________

Company Number: __________

V. INSTITUTIONAL BIOSAFETY COMMITTEES

Institutional Biosafety Committees (IBCs) are currently used by the National Institutes of Health (NIH), universities, and private companies t[o] implement NIH guidelines for research involving recombinant DNA molecules. The committees are responsible for reviewing research proposals using rDNA technology to ensure proper containment of recombinant organisms and the safety of laboratory personnel. IBCs may also perform other functions, including oversight of research on infectious diseases, hazardous chemical[s] or radioactive materials.

1. Do you currently have an IBC? _____

2. If yes,

   How many members does your IBC have? _____

   How long does it take them to make a decision on levels of containment, with time being measured as:

   -- elapsed time, or total time from request for review to final decis[ion] __________

   -- hours of discussion and consideration on each case __________

   Do you have separate liability insurance for your IBC? _____

   If so, what is the annual premium? $_________
   what is the coverage? $______________
   what is the type of coverage (e.g., risk retention or a private insurance company)? __________

Company Number: __________

VI. FIELD TRIALS

1. On average, how many different microorganisms do you expect will be field tested in order to develop one commercial product? _____

   How many field tests do each of these microoganisms undergo? _____

2. Do you expect that the estimates in the last question will increase, decrease or remain constant over the next five years? __________

3. Have your product development plans been delayed because there is no regulation in place for microorganism products in TSCA-related market areas? _______________